

## Is Kidney Transplantation for Everyone? The Example of the Older Dialysis Patient

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**For the average patient with ESRD, kidney transplantation improves quality of life and prolongs survival compared with patients who are on the transplant waiting list and remain on dialysis. Despite the proven benefits, some patient populations, such as those of older age, may not be referred and accepted for kidney transplantation to the same extent as younger patients. The population with ESRD is aging. Nearly half of all new patients are older than 65 yr. Nephrologists and transplant surgeons will need to make more and more decisions regarding transplantation referral and candidacy in this population. This article reviews the data on survival, quality of life, and cost-effectiveness of kidney transplantation in the older dialysis patient. Clinical guidelines and data on current practice are also reviewed.**

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The principal goals of kidney transplantation are to improve health-related quality of life and prolong survival. For the average patient with ESRD, the evidence to date confirms that these objectives are being achieved (1–3). In addition, from the perspective of the health care system, it would be ideal if these treatment goals were achieved in a cost-effective manner. Again, for the average patient, kidney transplantation is both less costly and more effective than the alternative of remaining on dialysis (1). Few health care technologies are this economically attractive, and thus considerable effort has been made to maximize transplantation for as many patients as possible.

The success in kidney transplantation has led to an increased demand for the procedure as well as the acceptance by some programs of “higher risk” candidates (4). In 2006, >350,000 patients were on maintenance dialysis in the United States with just over 100,000 new patients with ESRD entering the system each year (5). From this large cohort of patients, health care providers must decide who is an appropriate candidate for kidney transplantation. Specifically, which of the many patients with ESRD will enjoy an improvement in quality of life and survival if they receive a transplant. Poor or inappropriate selection of candidates may lead to adverse outcomes, a reduction in quality of life, a reduction in patient or graft survival, and an overall reduction in transplantation as a cost-effective treatment strategy. Selection for kidney transplantation is often straightforward for many patients, because there are very few

absolute contraindications, such as active infection or recent malignancy (6); however, there are many relative or potential contraindications, such as advancing age, obesity, peripheral vascular disease, and combinations of these, that are making decision-making increasingly more difficult (6,7). Of the factors to consider, the advancing age of the population with ESRD is becoming one of the most difficult to deal with in the transplant evaluation process.

As shown in Figure 1, the growth in the population with ESRD during the past 20 yr has occurred predominantly in those who are older than 65 yr (5). The adjusted incident rate of ESRD for patients who are  $\geq 75$  yr was 1744 per million population compared with only 127 per million population for those between 20 and 44 yr of age (5). In 2006, 49% of the incident population with ESRD were older than 65 yr, and 26% were  $\geq 75$  yr (5). It is now estimated that one of every 200 adults who are older than 75 yr in the United States has ESRD (5). Given that nearly half of new patients with ESRD are now  $\geq 65$  yr, nephrologists will need to decide which of these patients should be referred, and transplant programs will need to decide which patients to accept for transplantation.

### Patient Survival in Older Kidney Transplant Candidates

Before considering transplantation for older patients, it is important to ensure that their survival is not adversely affected by transplant surgery and the use of immunosuppression. In their seminal article, Wolfe *et al.* (3) demonstrated that patients who received a kidney transplant had a 68% reduction in mortality compared with those who remained on the waiting list. The survival advantage was confirmed in various subgroups, including age. For patients between the ages of 60 and 74 yr, there was a 61% lower mortality for

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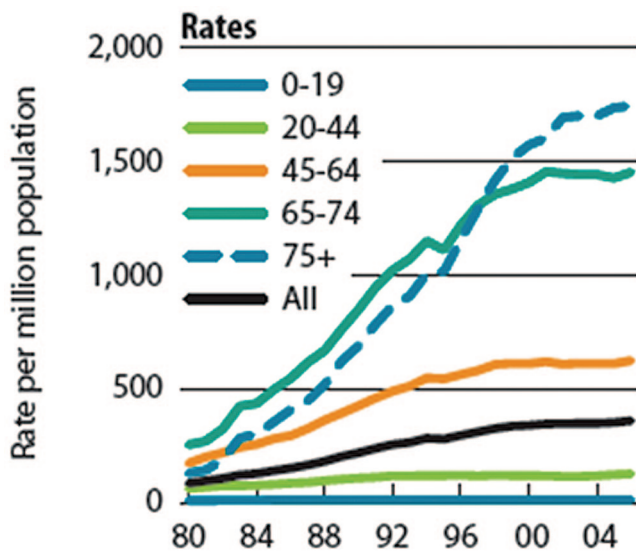


Figure 1. Incident rate of ESRD by age categories in the United States. Adapted from reference 5: U.S. Renal Data System: USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.

those who received a kidney transplant compared with the cohort who remained on the waiting list (3). This survival advantage translated into a projected increase in lifespan of 4 yr. Even those between the ages of 70 and 74 yr had a projected increase in survival of 1 yr with transplantation compared with remaining on dialysis (3). It should be noted, however, that only 13% of the transplant recipients were older than 60 yr in this analysis (3).

In a similar analysis to the original article by Wolfe *et al.* (3), Rao *et al.* (8) examined the survival of elderly kidney transplant candidates in the United States. They analyzed 5567 patients who were  $\geq 70$  yr and were placed on the kidney transplant waiting list between 1990 and 2004. Of these, 37% received a deceased-donor and 6% received a living-donor transplant. Overall, patients who received a kidney transplant had an adjusted relative risk (RR) for death of 0.59 (95% confidence interval [CI] 0.53 to 0.65) compared with those who remained on the waiting list (8). As shown in Figure 2, the RR for death varied with time after transplantation, being highest in the early posttransplantation period and decreasing thereafter. At 125 d after transplantation, the RR for transplantation equaled that of the waiting list but was lower from that time point onward (Figure 2) (8). Because of the high initial RR for death, survival of the transplant patients was worse than for the dialysis patients who were on the waiting list, until 1.8 yr after transplantation (Figure 3) (8). Subgroup analyses based on age showed a slight reduction in benefit for older patients; however, this remained statistically significant. For patients who were older than 75 yr, kidney transplantation was associated with an adjusted RR for death of 0.67 (95% CI 0.53 to 0.86) compared with those who remained on dialysis (8). A signifi-

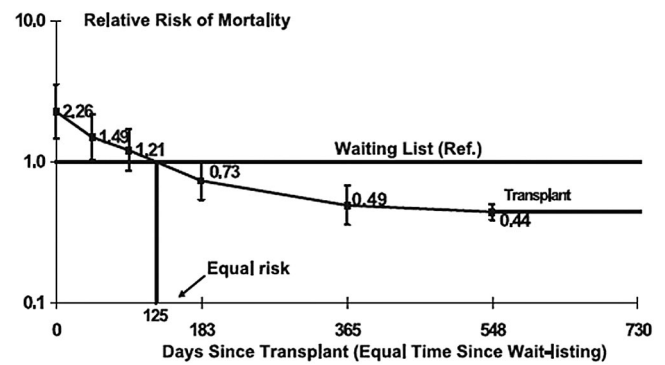


Figure 2. RR of mortality for transplant recipients versus dialysis patients on the waiting listed at  $\geq 70$  yr. At 125 d after transplantation, the transplant recipients and dialysis patients who were on the waiting list had an equal risk for death. The long-term mortality risk was 56% lower for the transplant recipients. Reprinted from reference 8 (Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK: Renal transplantation in elderly patients older than 70 years of age: Results from the Scientific Registry of Transplant Recipients. *Transplantation* 83(8): 1069–1074, 2007).

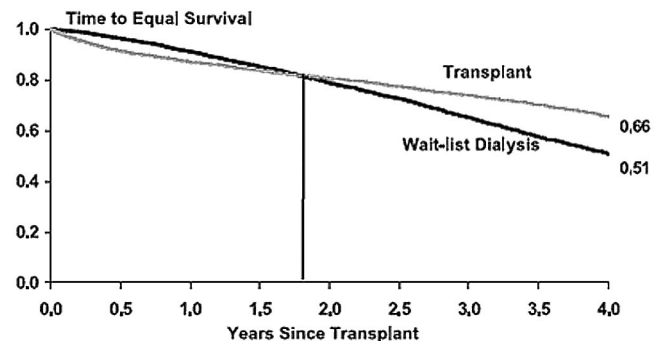


Figure 3. Cumulative survival curves for deceased-donor transplant recipients who were older than 70 yr and similarly aged dialysis patients who were on the waiting listed. Adjusted patient survival was 66% at 4 yr for the transplant recipients compared with 51% for the dialysis patients on the waiting list (8). Reprinted from reference 8 (Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK: Renal transplantation in elderly patients older than 70 years of age: Results from the Scientific Registry of Transplant Recipients. *Transplantation* 83(8): 1069–1074, 2007).

cant survival benefit persisted for patients with renal failure as a result of diabetes or hypertension as well as for patients who received expanded-criteria donor kidneys (8).

### Waiting Time and Survival for Older Transplant Recipients

A legitimate concern when determining transplant candidacy is whether the benefit of kidney transplantation will persist in older patients after a prolonged wait on dialysis. Gill *et al.* (9) examined this question in an analysis of 63,783 transplant candidates from the US Renal Data System database. Overall, they showed that patients who were older than 70 yr had an ex-

pected survival of 4.5 yr on the waiting list and 8.2 yr with a kidney transplant for a benefit of 3.7 yr (9). They found that the benefit of kidney transplantation decreased with time on the waiting list, but even after 3 yr of waiting, patients who were older than 70 still gained an additional 2.5 yr of life with transplantation. The analysis by Rao *et al.* showed that waiting time did not affect survival benefit in older transplant recipients (8). For patients from an organ procurement organization with long waiting time (>1350 d), kidney transplantation was associated with a 42% reduction in death ( $P < 0.0001$ ) compared with those who remained on the waiting list (8); therefore, it seems that waiting times in the range of 3 to 4 yr do not have a significant impact on the potential survival benefit in older transplant recipients. It is not known whether waiting times beyond this would result in poorer outcomes in this patient population, however.

### Quality of Life for Older Transplant Recipients

Health-related quality of life is significantly improved for the average kidney transplant candidate, but does this hold true for older patients? Laupacis *et al.* (1) evaluated quality of life before and after kidney transplantation in 168 patients using the Sickness Impact Profile and the time tradeoff technique for measuring utility. For the entire cohort, as well as the subgroup of patients who were older than 60 yr, the quality-of-life measures improved with transplantation. For example, the utility on dialysis was only 0.55 for patients who were older than 60 yr, and this increased to 0.72 with transplantation (0.75 for those who were younger than 60 yr) (1). Similarly, Humar *et al.* (10) found that quality for life for older kidney transplant recipients was remarkably good at 1 yr after transplantation using the SF-36 questionnaire. There were 149 patients who were younger than and 42 patients who were  $\geq 65$  yr (mean 69 yr) in the analysis (10). The older transplant recipients had quality-of-life scores that were comparable or even higher than age-matched values from the general US population for five of eight domains. Only the domains of physical functioning, role limitation as a result of physical health problems, and bodily pain scored lower than the national norms (10). Importantly, older transplant patients had scores for overall general health perception that were higher than the national age-matched norms and nearly identical to the transplant recipients who were younger than 65 yr (10).

### Cost-Effectiveness of Kidney Transplantation in Older Recipients

Laupacis *et al.* (1) showed that kidney transplantation was both more effective and less costly compared with remaining on dialysis. This finding was also confirmed in the subgroup of patients who were older than 60 yr. In this patient population, the annual cost of dialysis was \$65,720, whereas the cost of the first year after transplantation was \$63,708 (1); however, in year 2, the cost of transplantation was only \$21,160 (1). With longer follow-up, kidney transplantation would seem even more cost-

effective because the cost of dialysis remains relatively constant over time (1).

Jassal *et al.* (11) performed a decision analysis that examined the cost-effectiveness of transplantation in the elderly. Life expectancy and quality-adjusted life expectancy improved with transplantation in all age groups (ages 60 to 85) and with varying waiting times (11). The economic results, however, were not as favorable for all patient subgroups. Receiving a living-donor kidney transplant was an economically attractive option for any patient, regardless of age. In contrast, receiving a deceased-donor transplant after a 2-yr wait was not economically attractive for those who were older than 75, because the cost per quality-adjusted life-year (QALY) was \$99,553 to \$231,158 (11). If the waiting time were extended to 4 yr, then kidney transplantation was not economically attractive for any age group with the cost per QALY ranging from \$175,107 to \$14,585,442 (11). In this analysis, the findings were very sensitive to waiting time (11), suggesting that, from an economic perspective, living-donor transplantation might be the preferred treatment option for older transplant candidates.

### Clinical Guidelines on Kidney Transplantation in Older Patients

Practice guidelines from major medical societies support transplantation of older patients with ESRD. The American Society of Transplantation guidelines on the evaluation of renal transplant candidates state that “there should be no absolute upper age limit for excluding patients whose overall health and life situation suggest that transplantation will be beneficial” (7). They do, however, recommend that older candidates be screened more aggressively for cardiovascular disease and malignancy (7). Similarly, the Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation state that “advanced age *per se* is not a contraindication to kidney transplantation” (6). The guidelines, however, go on to state that “transplant candidates should have a reasonable probability of surviving beyond current waiting times for transplantation, given the resources required to assess and maintain patients on the renal transplant waiting list” (6). In a similar manner, the UK Renal Association guidelines state that “age is not a contra-indication to transplantation, but age related comorbidity is an important limiting factor” (12). These guidelines all suggest that physiologic age and burden of coexisting conditions are far more important than chronological age and that detailed evaluation in this population is warranted (6,7,12).

### Practice Patterns for Evaluation and Listing of Older Candidates for Kidney Transplantation

Although all major guidelines support the notion that age should not limit access to kidney transplantation, it is not clear whether this is translating into clinical practice. Since 2005, nearly 4000 patients who were older than 65 yr have been added to the kidney waiting list each year in the United States (13). In 2008, approximately 15% of new additions to the waiting list were older than 65 yr, and currently 17% of the patients

who are on the kidney waiting list are older than 65 yr (13). These numbers are relatively small considering that approximately half of all new patients with ESRD are older than 65 yr and confirm a high degree of selection in this age group. In contrast, only 23% of the current dialysis population is younger than 50 yr, but this population comprises 43% of the waiting list (5). Viewed another way, approximately 7% of dialysis patients who are older than 65 are on the waiting list compared with 36% of those who are younger than 50 (5).

In an analysis of 4523 patients who started renal replacement therapy in Scotland, age was an important determinant of access to the transplant waiting list (14). Patients who were older than 65 yr had a 93% (95% CI 92 to 94%) lower likelihood of being placed on the transplant waiting list compared with patients who were aged 18 to 34 (14). This analysis, however, was limited by the lack of full adjustment for specific comorbid conditions (14). Villar *et al.* (15) examined transplant referral practices from three separate nephrology practices in France. Once again, age was an important determinant of access to transplantation, and no patient who was older than 70 yr was even referred for transplantation evaluation in this cohort (15). After adjustment for many covariates, including cardiovascular disease, diabetes, and malignancy, patients who were older than 65 yr were 93% (95% CI 80 to 97%) less likely to be placed on a transplant waiting list than those who were younger than 50 yr (15). In addition, 9% of the cohort had no obvious contraindication to transplantation but were not referred (15). Ninety-four percent of these patients were older than 60 yr, and none died within 1 yr of starting dialysis (15).

Kiberd *et al.* (16) showed that age was the most important discriminating factor for determining referral for transplantation. In a series of consecutive patients with ESRD they found that 58% were not referred for transplantation, and of these, 40% had no contraindication to transplantation according to published guidelines (16). Patients who were not referred and who had no contraindication were older ( $75 \pm 7$  versus  $50 \pm 12$  yr;  $P < 0.0001$ ) and had higher comorbidity scores compared with the referred patients without contraindication (16); however, in multivariate analysis, age was the only significant factor associated with not being referred for transplantation when no contraindication was present (16). Receiver operating characteristic curve analysis showed that age alone ( $c = 0.99$ ; 95% CI 0.97 to 1.00) was far more discriminate at determining transplant candidate status than three different comorbidity scores, including the Charlson Comorbidity Index (16).

## Controversies Regarding Transplantation in Older Dialysis Patients

That such a small proportion of older dialysis patients are actually listed and receive a kidney transplant confirms that a high degree of selection is occurring in this process. As such, the studies reviewed here dealing with outcomes (specifically survival and quality of life) may be hindered by a degree of selection bias. This will not be known for certain unless we perform the natural experiment of significantly increasing the referral, acceptance, and *actual transplantation* of older patients with renal failure.

Why has this not already occurred? There are four, perhaps more, possible explanations. First, it is possible that the older patients who are not referred and accepted for transplantation are actually not candidates on the basis of medical contraindications. There are, unfortunately, few data to support this possibility. Second, older patients may not perceive themselves as potential transplant candidates and may decline this option or not seek it as frequently as younger patients. We need more research to answer this question. Third, physicians might be reluctant to refer or accept older patients for transplantation because of rising waiting times and the possibility that they may never receive a transplant. In a recent analysis that involved candidates who were on the waiting list and were older than 60 yr, Schold *et al.* (17) projected that 46% who were listed after 2006 will die before receiving a deceased-donor transplant. Fourth and perhaps most difficult, physicians may be uncomfortable referring and accepting older candidates for transplantation knowing that the donor pool is limited and that they might “displace” a kidney from a younger recipient.

The final point noted pertains to both acceptance on the waiting list and allocation of a kidney once on the waiting list. Curtis (18) wrote of ageism sneaking into our transplantation system as an unintended consequence of official policy. Although Curtis was discussing age-based discrimination in the context of organ *allocation* (18), it is possible that ageism may also be at play in the process of referral and acceptance of patients with renal failure as candidates for kidney transplantation. Taking a slightly different perspective in a complementary article, Danovitch (19) suggested that age discrimination is not the issue and that we need in place policies that protect all of our patients, young, middle aged, and elderly. Although there has been much open debate and discussion around proposals to change the allocation of deceased-donor kidneys, it is obvious but rarely discussed that patients cannot be allocated to receive a kidney transplant if they are never referred or placed on a waiting list. This is where the controversy between allocation and acceptance differs. Allocation algorithms are objectively defined, publicly debated, and formally adopted into practice. Although there is always the possibility of “gaming” the system, allocation is generally governed by stronger oversight than referral and acceptance for transplantation. This latter practice remains under the complete control of referring physicians and individual transplant programs. Although guidelines for transplant candidacy exist, these are merely guidelines that are not enforced (6,7). Referral and acceptance for transplantation is rarely, if ever, audited to determine whether current guidelines are being followed. If we are to move forward in an open and transparent manner, then policies and decision-making around referral and acceptance of older dialysis patients needs the same attention as the issue of allocation.

## Conclusions

As with the general population, the population with ESRD is aging. Nearly half of all new patients are older than 65 yr. Nephrologists and transplant surgeons will need to make more and more decisions regarding transplantation referral and can-

didacy in this population. The data to date suggest that older transplant recipients, even those who are older than 75 yr, have improved mortality compared with similarly aged candidates who remain on the waiting list. This survival benefit, however, is not realized until approximately 2 yr after transplantation. In addition, quality of life and QALYs are improved in older transplant recipients. From a health systems perspective, modeling suggests that transplantation remains a cost-effective strategy for all older patients when living donors are used or when deceased donation can occur with short waiting times.

Until further evidence emerges, nephrologists should continue to view all of their older patients with ESRD as potential transplant candidates. If functional status is reasonable and no obvious contraindication is present (e.g., recent malignancy), then transplant evaluation should proceed with screening for cardiovascular disease and malignancy as suggested by guidelines. Transplant programs in turn need to view older patients with ESRD as acceptable candidates if no contraindication emerges during the evaluation process. The decision regarding eligibility for transplantation must be made in the best interests of the patient and be based on objective medical and surgical criteria. An open evaluation process without the use of rigid age cutoffs is the only way to ensure that ageism does not overtake the transplant evaluation process. Further research and public debate on the evaluation and acceptance of older patients for transplantation are needed to determine better, using objective criteria, which older patients are best served by transplantation.

## Disclosures

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